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DCIEM SL 2000 053

ORIGINAL RESEARCH

Melatonin and Zopiclone as Pharmacologic Aids to Facilitate Crew Rest

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PAUL MA, BROWN G, BUGUET A, GRAY G, PIGEAU RA, WEINBERG H, RADOMSKI M. *Melatonin and zopiclone as pharmacologic aids to facilitate crew rest.* **Aviat Space Environ Med 2001; 72:974–84.**

Purpose: In response to mission imperatives, transport aircrews must often sleep at inappropriate circadian times resulting in inadequate sleep. This study was undertaken to determine whether either melatonin or zopiclone could facilitate early circadian sleep, and to assess whether either of these medications would result in a psychomotor performance decrement which would preclude their use in aircrew. ***Method:*** Thirteen subjects from DCIEM completed a double-blind cross-over protocol. All subjects were assessed for psychomotor performance during 3 drug conditions (placebo, 10 mg melatonin, and 7.5 mg zopiclone), which were separated by one week. Each of these conditions involved 2 nights of sleep, back-to-back, with the first night being a normal circadian control sleep (23:00 h bedtime, arising at 06:45 h), and the second night being an early circadian drug sleep (drugs at 16:45 h, 17:00 h bedtime, arising at 23:45 h). All subjects were tested for psychomotor performance, on both nights of each of the 3 drug conditions, pre- and post-sleep. Further, during the early circadian drug night, all subjects were tested every hour after arising at 23:45 h (24:00 h until 07:00 h. At the beginning of each psychomotor test session, subjects were asked for their subjective levels of sleepiness and fatigue. ***Results:*** Relative to placebo (339.5 min) the subjects slept more on melatonin (370.2 min, $p < 0.01$), and zopiclone (373.3 min, $p < 0.01$). Performance in serial reaction time (SRT) task ($p < 0.001$), logical reasoning task (LRT) ($p < 0.001$), serial subtraction task (SST) ($p < 0.02$), and Multitask (MT) ($p < 0.03$) were impaired for all 3 drug conditions immediately on awakening, compared with pre-sleep performance, as a result of a sleep-inertia effect. With respect to the subjective data, sleep inertia effects were evident for sleepiness ($p < 0.001$), mental fatigue ($p < 0.002$), and physical fatigue ($p < 0.05$). For SRT, LRT, and SST, performance recovered to pre-sleep levels within 1.25 h of awakening, and for MT recovery occurred 2.25 h after awakening. There were no differences in performance or subjective measures between placebo, melatonin and zopiclone. ***Conclusions:*** Both zopiclone and melatonin improved sleep relative to placebo. After sleep inertia, performance recovered to pre-sleep levels for all tasks and was sustained at that level throughout the balance of the testing period. There was no impact of melatonin or zopiclone on performance measures compared with placebo.

Keywords: crew rest, sleep problems, pharmaceuticals, psychomotor performance.

IN A RECENT STUDY, we monitored 10 CC130 resupply missions to the former Yugoslavia (33). During that study we measured aircrew performance in the air (using computer-based psychomotor test batteries) and sleep hygiene throughout the mission (using wrist actigraphs). Analyses of those data confirmed a significant impact of fatigue on psychomotor performance during the long transatlantic flights. Further, during their second night in the United Kingdom, due to the operational schedule, the crews had to sleep at inappropriately early circadian times, relative to their home base and, therefore, had difficulty getting sufficient sleep.

The provision of ample opportunity for crew rest between successive legs of long transmeridian missions is the first line of defense against the development of fatigue and the accrual of sleep debt. However, the operational imperatives that drive military taskings often preclude such scheduling concessions. In such situations, appropriate pharmacologic intervention has the potential to improve crew rest and, therefore, sustain crew performance.

Literature Review

Melatonin

Melatonin is a naturally occurring hormone synthesized by the pineal gland from the precursor amino acid tryptophan (8). In pharmacologic doses, melatonin has a large margin of safety (8), producing a mild soporific effect with minimal side-effects. This along with melatonin's ability to advance or retard circadian rhythms depending on the dosage and the timing of ingestion (3,8) has resulted in increased research interest. Several studies suggest that melatonin is able to adjust circadian rhythms and reduce the effects of jet lag on cabin crew (34) or passengers (3,17). Dawson and Armstrong (14) refer to melatonin as a chronobiotic because of its ability to advance or retard circadian rhythms. Other studies have demonstrated the hypnotic effect of melatonin (17,26) in a laboratory environment. The effects

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This manuscript was received for review in May 2000. It was revised in February and May 2001. It was accepted for publication in May 2001.

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of melatonin on human performance are controversial. One recent study showed that aircrew who were administered melatonin on a long transmeridian mission had improved sleep patterns and fewer errors on a choice reaction task after arrival (11). Several studies have concluded that melatonin does not act as a hypnotic in the classic sense, but rather as a sleep-promoting agent (14,24,37). In a recent review paper Caldwell (9, p. 243) stated that "Performance in a laboratory shows that reaction time is slowed and sleepiness is increased when tests are given 30 min to 2 h after melatonin administration. However, if taken before a night's sleep, then melatonin does not seem to adversely affect next-morning performance." Caldwell (9) also states that "Melatonin appears to open the 'sleep gate' when circumstances are right for sleep, but does not induce sleep."

Some studies have documented small decrements in simple auditory reaction time and visual serial choice reaction time (17,49) whereas another study (3) found no difference in a logical reasoning task or in a letter cancellation task. A study by Lieberman (26) reported a slowing of reaction time but a decrease in errors of commission on this task. This study also found that sustained fine motor performance, memory and sensitivity were not impaired by melatonin. One hour after ingestion of a 5-mg dose of melatonin, Suhner et al. (42) assessed 20 healthy subjects in a standardized computer test battery to assess driving skills such as attention, reaction time, power of concentration and sensorimotor coordination. They found that just one of the 16 variables, selective attention, was significantly affected by melatonin, and even those values were within the normal range. Slotten and Krekling (40) used logical reasoning, serial addition/subtraction, visual-spatial and four-choice reaction time tasks to assess performance after ingestion of a 1.6-mg dose of melatonin. They found no effect on performance speed and accuracy during the post ingestion melatonin peak (about 35 to 95 min after ingestion), but found that during the temperature trough (240 to 300 min after ingestion), reaction times to the serial addition/subtraction task increased by about 45 ms. They postulate that this was due to melatonin's hypothermic properties which caused a slowing of cerebral processing speed. While this is interesting work, the major limitation of the study is the single subject, double-blind, alternating treatments design. The study should be repeated with multiple subjects, using a repeated-measures, double-blind crossover protocol in order to confirm these interesting results. Lieberman et al. (26) gave 14 subjects three 80 mg doses of melatonin, 1 h apart, and found a slowing of reaction time (about 23 ms) but a concurrent decrease in errors of commission. This apparent sacrifice of speed for accuracy suggests that the subjects simply shifted their performance on the speed/accuracy curve. Zhdanova et al. (50) used evening doses of 0.3 or 1.0 mg of melatonin to significantly reduce sleep latency and there was no impact of melatonin on either simple or 4-choice reaction time on the morning after treatment. Dollins et al. (17) used 20 male subjects on 5 separate occasions with melatonin doses of 10, 20, 40, 80 mg or placebo, administered at 11:45 h. They observed significant decreases in the number of correct responses to an auditory vigilance task within 15 min of ingestion for all melatonin doses as well as 2 h and 15 min post ingestion. Four-choice reaction time latencies also increased significantly during the melatonin treatments.

Comperatore et al. (12) performed two studies using 20 female subjects in each between-groups study. In their first study, the subjects were administered a 10 mg dose of melatonin or placebo at 23:00 h for 7 d. The subjects were awakened at 06:30 h for psychomotor testing which continued until 18:30 h. The melatonin subjects appear to have made more errors on the 4-choice reaction time task than the placebo subjects from 6 to 12 h after ingestion, but because their figures of performance results do not show standard error bars, it is difficult to appreciate the difference in performance between these 2 groups of subjects. In view of the Slotten and Krekling results (40) it would have been interesting to determine the location of the core body temperature trough for these data. In the second Comperatore study (12) the subjects were given a 10 mg dose of melatonin or placebo at 13:00 h for 5 d. The subjects slept 8 h from 16:30 h to 00:30 h and were tested after awakening at 01:30 h, 03:30 h, and 06:10 h. The melatonin subjects made significantly more errors than the placebo subjects when tested at 01:30 h (1 h after awakening), but not in the 2 subsequent test sessions. Again, because the graphed performance results do not show standard error bars, it is difficult to appreciate the extent of any melatonin-induced increase in errors on this task.

Zopiclone

Zopiclone (Imovane®) is a cyclopyrrolone derivative with a half-life of approximately 5 h (18,25) that produces a short-acting sedative/hypnotic effect. Daurat et al. (13) used a 7.5-mg dose of zopiclone to accelerate readjustment of the rest/activity cycle and to normalize the phase relationship between sleep and temperature rhythm after a westward flight across five time zones. They concluded that zopiclone exerted its "resetting" effects on jet lag desynchronosis by facilitating sleep induction rather than via a chronobiotic action. Griffiths et al. (19) used the Stroop task, serial reaction time, and logical reasoning tasks as well as saccadic eye movement in response to a 7.5-mg dose of zopiclone and found impaired saccadic eye movement up to 3 h after ingestion. Memory was not affected, and 6 h after ingestion, there was no evidence of any other effect. In contrast, Nicholson and Stone (31) conducted a dose-response study of zopiclone (2.5, 5.0, 7.5 and 10 mg) using a digit-symbol substitution and symbol copying tasks to measure performance 9 h after ingestion. They found an 8% decrease in substitutions at the 7.5 and 10 mg doses but not at the 2 lower doses. They also found less than a 7% decrease in symbol copying at the 10-mg dose, but not for the 3 lesser doses.

Virtually all studies assessing zopiclone report an effective hypnotic response. Using a 7.5-mg dose (the standard clinical dose), various studies (6,7,21,25,39,41,43) have been unable to demonstrate residual effects of zopiclone

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on various aspects of psychomotor performance. O'Hanlon et al. (32) used a car driving task to evaluate a 7.5 mg dose of zopiclone for two consecutive nights and found slightly impaired performance among 16 female subjects during the morning, 10 h after drug ingestion. Several studies investigated the residual effects of zopiclone beginning almost immediately after ingestion (1,19,28,36,41,44). Subjan and Hindmarch (41) found increased reaction times for a memory scan task, 1 h after drug ingestion, but no impact on performance 10 h after ingestion. Warot et al., (44) used flicker fusion, choice reaction time, digit symbol substitution, and memory tests to find no impairment beyond 6 h after ingestion. Mattila et al. (28) assessed simulated driving, divided attention, digit-symbol substitution, symbol copying, flicker fusion and body sway in response to 7.5 mg zopiclone. They found increased tracking error and prolonged reaction times at 1.5 h, reduced substitutions at 1.5 and 3.5 h, with lowered threshold flicker fusion and increased body sway. There was impaired memory after 3.5 h but no effects were present at 6 h.

The objective of the present study was to induce sleep and monitor sleep quality during an inappropriately early circadian time (similar to the sleep imperatives encountered by aircrew during overseas air transport operations). Our specific interests were to evaluate the efficacy of melatonin and zopiclone in improving early circadian sleep, and to determine whether or not there would be a performance liability associated with either drug immediately on awakening as well as throughout a 7-h post-sleep psychomotor test period. Further, we wanted to determine whether or not there would be any potentiation of the normal sleep inertia effect (transient impaired performance occurring immediately after awakening) with either melatonin or zopiclone.

METHODS

The study protocol was approved by the DCIEM Human Ethics Committee.

There were 14 volunteer male subjects between 22 and 50 yr of age who passed a screening medical, provided written informed consent, and were studied in a double-blind repeated-measures design in which subjects received all three drug treatment conditions in a counterbalanced order. One subject did not complete the study. The three drug conditions were placebo (lactose monohydrate powder), zopiclone 7.5 mg, and melatonin 10 mg. The 10-mg dose of melatonin consisted of 5 mg pure melatonin (from Biosynth International Inc, Naperville, IL) to facilitate initial sleep, together with 5 mg of controlled-released melatonin (Circadin®, Neurim Pharmaceuticals, Tel Aviv, Israel), to sustain sleep. Melatonin is classified as an "investigative new drug" in Canada, and regulatory approval was granted for its use in this investigation. All study medications were made up in identical gelatin capsules by the chief pharmacist at the Clarke Institute of Psychiatry (Toronto, ON), who also generated the medication code. The medication code was revealed only at the end of the study, after all the data were collected.

To avoid any confounding due to circadian influences, all subjects were asked to avoid long transmeridian flights in the 2 wk prior to the study and to maintain regular sleep/waking schedules during the week prior to the study. Therefore all subjects were asked to wear wrist actigraphs (Precision Control Design Inc., Fort Walton Beach, FL) which contain a small accelerometer to detect body movement such that a waking state can be differentiated from a sleeping state (35).

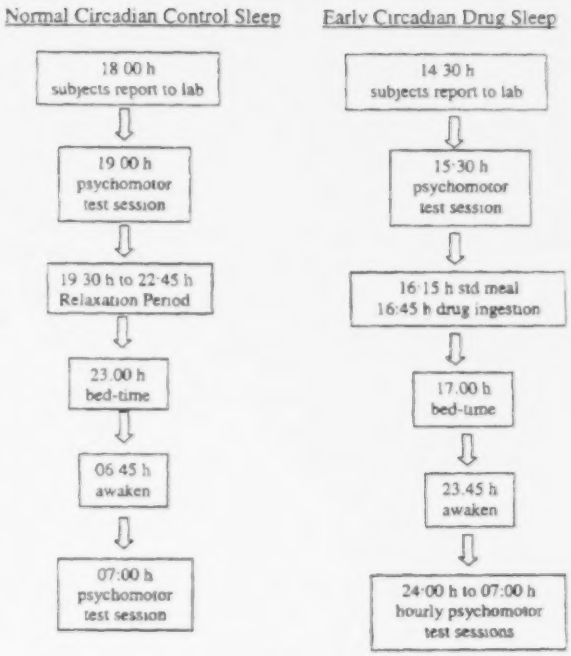

Fig. 1. Schematic of events/times for experimental sessions.

The subjects were asked to avoid taking medications, alcohol and sleeping pills for 36 h prior to the study. Subjects were also instructed to avoid using caffeine (coffee, tea, soft drinks, and chocolate) for 6 h prior to each experimental session.

Four subjects were tested concurrently in a 4-wk protocol, resulting in three groups of four subjects and one with two subjects. The repeated-measures protocol was identical for all subjects. The first week was a baseline session designed to familiarize the subjects with the requirement to sleep in the laboratory and to collect baseline data. During this session, subjects slept in the laboratory, at normal circadian time (23:00 h to 06:45 h), for 2 consecutive familiarization nights and underwent one psychomotor testing iteration before sleep and again within 15 min of awakening.

During each of the next 3 wk, one experimental session (placebo, zopiclone, or melatonin in counterbalanced order) per week was conducted for each group of 4 subjects. These sessions involved 2 consecutive nights; a normal circadian drug-free control sleep night, (23:00 h to 06:45 h), followed the next day by an early circadian drug sleep, (17:00 h to 23:45 h). One week between sessions was allowed for drug "wash-out". The events and timings for the experimental sessions are illustrated in **Fig. 1.**

As illustrated in Fig. 1 the subjects began an extended

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period of psychomotor testing on awakening from their early circadian sleep period. Each performance session lasted about 30 min providing the subjects with 30 min rest each hour. However, they were not allowed to sleep during this interval. After the second post-sleep performance assessment, subjects were provided a standardized snack.

Immediately before commencing each psychomotor test session, a 1-min computer questionnaire presented on the same lap-top computers asked for the following subjective assessments: a) alertness by selecting the most appropriate response from the 7-point Stanford Sleepiness Scale (23); b) mental fatigue state by selecting any number on a continuous scale from 1 (very mentally fresh) to 7 (very mentally fatigued) (20); and c) physical fatigue state on a continuous scale from 1 (very physically fresh) to 7 (very physically fatigued) (20).

During the psychomotor performance sessions, the following tasks were presented: a) three psychomotor tests from the DCIEM SUSOPS (sustained operations) test battery (2,4) were performed in the following order; Serial Reaction Time (SRT) (47) for three minutes, Logical Reasoning Task (LRT) (4) for 3 min, and Serial Subtraction Task (SST) (22) for 3 min; followed by b) a multitask (MT) designed to simulate the information processing characteristics of flight performance (46) and taking 15 min per data collection iteration. The task simulated flying an aircraft to specific targets or "waypoints." The computer screen showed four separate displays representing four sub-tasks to be performed simultaneously. Three of these four tasks interacted. There were vigilance sub-tasks with altitude assignment changes visible for only 5 s and the pilots also had to be vigilant in order to determine when the two "attitude indicators" disagreed with each other and then determine which of the attitude indicators accurately reflected the "aircraft attitude." A bar task (analagous to managing the power quadrant of a large multi-engine transport) did not interact with the other three sub-tasks. The measures of performance include scores related to error detection and selective attention, visuo-motor tracking and co-ordination, short-term memory, mental arithmetic, and scanning strategies. The raw output data file was merged with a computer reduction algorithm to yield a single final weighted composite score which reconciles correct responses and errors. This task is explained in more detail elsewhere (46).

The SUSOPS tests have a history of well-documented laboratory-based validations concerning the effects of fatigue on performance (2,4). Thus it was considered important to include these tasks to compare data obtained in this study to the existing literature. To assess higher order cognitive function and use a test with greater face validity to flying, the multitask was also used.

Lighting conditions in the psychomotor testing suite were kept constant (blackout curtains were used with fixed florescent lighting similar to the illumination found in a well-lit reading room) during psychomotor testing to preclude any effect of variation in lighting conditions on endogenous melatonin levels.

All subjects were trained to asymptote levels of performance by performing 12 iterations of the psychomotor tasks within the week prior to the study. The subjects slept in separate bedrooms in which the windows were covered with blackout curtains, creating a consistently dark sleep environment.

Although other measurements were taken, these data will be reported in separate publications. These measures include 40 Hz EEG recordings taken during psychomotor test sessions, continuous core temperature via radio pills, sleep recordings via actigraphic mattresses during bed rest, and neuro-endocrine samples (melatonin from saliva as well as 6-sulfatoxymelatonin and cortisol from pooled urine).

Statistical Analysis

All data were submitted to standard parametric analyses of variance with repeated-measures. The actigraph data were analyzed using a 2-factor (3 levels of drugs × 2 levels of circadian sleep period) repeated-measures analysis of variance. The subjective and psychomotor data were analyzed in the following three groups of trials: a) in order to quantify sleep-inertia, pre- and post-sleep data are compared for the normal circadian control sleep (19:00 h and 06:45 h) and the early circadian drug sleep (17:00 h and 23:45 h), using a 3-factor [3 levels of drugs × 2 levels of circadian period × 2 levels of trials (pre- and post-sleep)] completely within-subjects repeated measures analysis of variance; b) to assess recovery from sleep-inertia, the 15:00 h, 24:00 h, and 01:00 h trials for the early circadian drug sleep are compared using a 2-factor (3 levels of drugs × 3 levels of trials) completely within-subjects repeated measures analyses of variance; and c) the post-sleep trials of the early circadian drug night from 01:00 h to 07:00 h are compared in order to determine to what extent subjects' psychomotor performance changed over the course of their all-night vigil. This 'c' comparison was accomplished with a 2-factor (3 levels of drug × 7 levels of trials) completely within-subjects repeated measures analysis of variance. Further, for the 'c' comparisons we also performed orthogonal polynomial analyses in order to look for linear, quadratic, and cubic trends in the data over time.

The Least Significant Difference Test was used to assess planned comparisons. The acceptable level of significance for all main effects or interactions was 0.05.

RESULTS

Sleep Duration and Quality

The normal circadian control sleep period (23:00 h to 06:45 h) was 465 min long while the early circadian drug sleep period was (17:00 h to 22:45 h) 405 min. To standardize the comparison, the last 60 min of the normal circadian control sleep period were not included in the analysis.

The software to analyze the wrist actigraph recordings was a program called 'Action W' (Ambulatory Monitoring Inc., Ardsley, NY). In order to score sleep this program used an algorithm to compute a weighted

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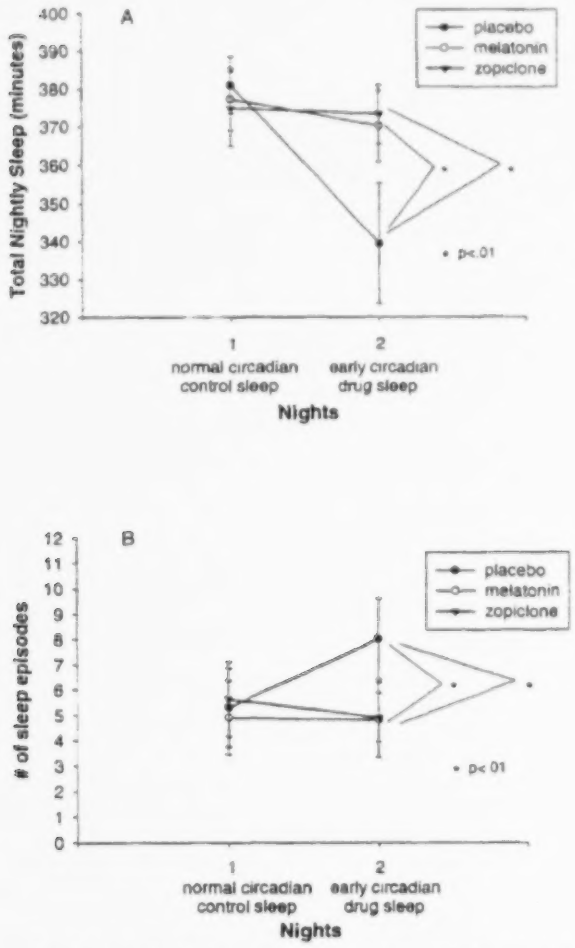

Fig. 2. Total nightly sleep and number of sleep episodes (mean ± SEM) across drugs for normal circadian control night and early circadian drug night

sum of the activity in the current minute, the preceding 4 min, and the following 2 min as follows:

$$S = 0.0033*(1.06*an4 + 0.54* \text{ and } 3 + 0.38*an2 - 0.76*an1 + 2.3*a0 + 0.74*a1 + 0.67*a2)$$

where an4 –an1 are activity counts from the prior 4 min, a0 is the current minute and a1 and a2 are the following 2 min (10,38).

The current minute is scored as sleep if $S > 1$.

The number of minutes spent asleep during each of the normal circadian control and early circadian drug nights is plotted in **Fig. 2a.** Of the 405 min available for sleep, subjects slept an average of 378 min (pooled data) during the control sleep. Total sleep time data were submitted to a 2-factor (3 levels of drugs × 2 levels of circadian sleep period) repeated measures analysis of variance. This analysis yielded a significant drugs × circadian sleep period interaction $F(2,26)=3.62$, $p < 0.04$. Post hoc analysis revealed that during early circadian sleep subjects slept more on melatonin (31 min) and zopiclone (34 min) than on placebo ($p < 0.01$). With both melatonin and zopiclone, subjects lost no sleep during the early circadian compared with the normal circadian condition.

The number of sleep-episodes (periods of sleep uninterrupted by wake) during each of the normal circadian and early drug nights are plotted in Fig. 2b. These data were submitted to the same 2-factor analysis of variance as the total sleep time data. There was a significant interaction drugs × circadian sleep period interaction $F(2,26)=3.24$, $p < 0.05$. Post hoc analysis revealed that during early circadian sleep, subjects on placebo had significantly more sleep episodes (awakenings) than when they were on melatonin or zopiclone ($p < 0.01$). While on melatonin or zopiclone, subjects had no more awakenings during early circadian sleep than during normal circadian sleep.

Psychological Data

Data from the questionnaire and psychomotor performance are presented in the following three groups of analyses: a) to quantify sleep-inertia, pre- and post-sleep data are compared for the normal circadian control sleep (19:00 h and 06:45 h) and the early circadian drug sleep (17:00 h and 23:45 h); b) to assess recovery from sleep-inertia, the 15:00 h, 24:00 h, and 01:00 h trials for the early circadian drug sleep night are compared; and c) the post-sleep trials of the early circadian drug night from 01:00 h to 07:00 h are compared in order to determine to what extent subjects' psychomotor performance changed over the course of their all-night vigil.

Subjective Data

Subjective assessments of sleepiness (Stanford Sleepiness Scale) and fatigue are plotted in **Fig. 3.** The pre- and post-sleep differences in alertness and fatigue (comparison a) were submitted to a 3-way (3 levels of drugs × 2 levels of circadian period, × 2 levels of trials (pre- and immediate post-sleep) repeated measures analysis of variance. The pre- to post-sleep increases in Stanford Sleepiness Scale were significant $F(1,12)=44.86$, $p < 0.0001$, as were the pre- to post increases in Mental Fatigue $F(1,12)=16.03$, $p < 0.002$, and in Physical Fatigue $F(1,12)=4.94$, $p < 0.05$. These results indicate a significant subjective degree of sleep-inertia on arising for each of the normal control and early circadian drug sleeps. There were no differential drug effects on the sleep-inertia.

The trials from 15:00 h, 24:00 h and 01:00 h of the early circadian drug night (comparison b) were submitted to a 2-way (3 levels of drug × 3 levels of trials (pre-sleep immediate post-sleep, and 1 h post awakening) repeated measures analysis of variance. The results indicate a significant main effect of trials for the Stanford Sleepiness Scale $F(2,24)=25.38$, $p < 0.00001$, Mental Fatigue $F(2,24)=11.16$, $p < 0.0004$, and for Physical Fatigue $F(2,24)=6.89$, $p < 0.004$. Post hoc analyses revealed that the increased subjective assessments of sleepiness and mental fatigue evident at 24:00 h improved by 01:00 h, and approached the pre-sleep levels taken at 15:00 h.

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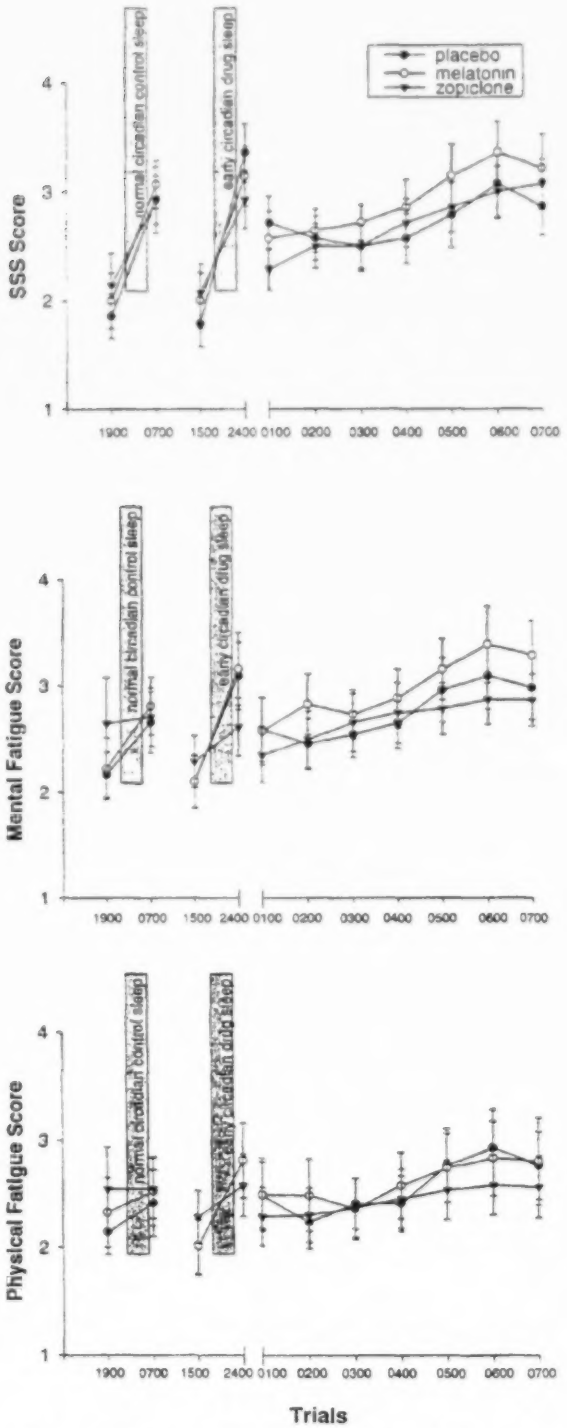

Fig. 3. Subjective assessments of sleepiness and fatigue (mean ± SEM) across drugs and trials for normal circadian control night and early circadian drug night.

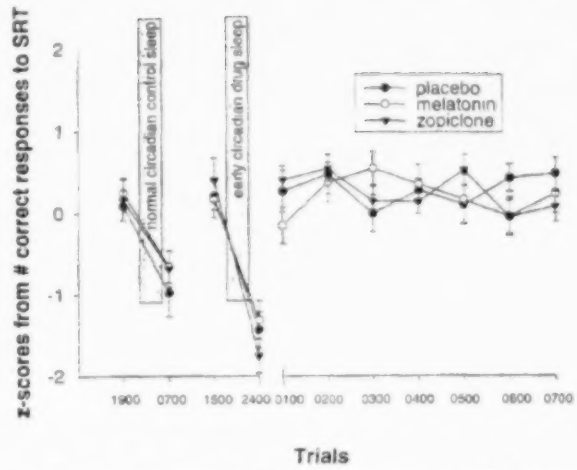

Fig. 4. z-scores fornumber of correct responses to Serial Reaction Time (SRT) task (mean ± SEM) plotted over drugs and trials for normal circadian control night and early circadian drug night.

Trials from 01:00 h to 07:00 h (comparison c) were submitted to a 2-way (3 levels of drug × 7 levels of post-sleep trials) repeated measures analysis of variance. The results indicate a significant main effect of trials for the Stanford Sleepiness Scale

$F(6,72)=5.68$, $p < .0001$, Mental Fatigue $F(6,72)=5.14$ $p < .0002$, and Physical Fatigue $F(6,72)=2.61$, $p < 0.024$. Polynomial analysis on the trials from 01:00 h to 07:00 h reveals a significant cubic effect for Stanford Sleepiness Scale $F(1,38)=7.11$, $p < 0.01$, for Mental Fatigue $F(1,38)=4.50$, $p < 0.04$, and for Physical Fatigue $F(1,38)=15.43$, $p < 0.003$. These cubic functions indicate that subjective levels of sleepiness, mental and physical fatigue were similar between 01:00 h and 03:00 h, after which they slowly increased until 06:00 h. The sleepiness and fatigue levels improved from 06:00 h to 07:00 h. This improvement in subjective sleepiness and fatigue levels is probably due to the energizing effects the subjects experienced by knowing that their all-night vigil was almost completed and they were about to be released on completion of this last psychomotor test session. There were no main effects or interactions involving either zopiclone or melatonin on any of these subjective variables.

Psychomotor Data

Serial Reaction Time (SRT): The SRT results are illustrated in **Fig. 4.** The pre- and post-sleep differences in SRT were submitted to the 3-way repeated measures analysis of variance (comparison a) using the number of correct responses as the independent variable. A completely repeated-measures analysis of variance reduces overall variability by removing between-subject differences from the error term. The serial reaction time results are illustrated in Fig. 4. Note that Fig. 4–8 are graphed with z-scores in order to better demonstrate the within subjects treatment effects. The analyses of variance were equivalent whether done with z-scores or with original units. Neither melatonin nor zopiclone

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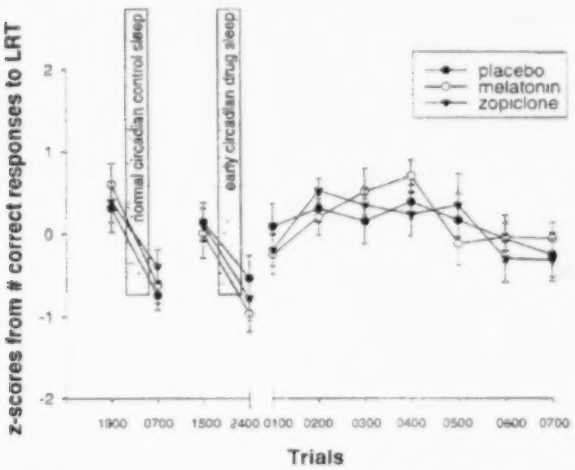

Fig. 5. z-scores for number of correct responses to Logical Reasoning task (LRT) (mean ± SEM) plotted over drugs and trials for normal circadian control night and early circadian drug night.

had any effect on SRT. There was a significant difference in pre- and post-sleep performance $F(1,12)=10.57$, $p < 0.007$ a main effect of circadian period $F(1,12)=22.46$, $p < .0005$), and a significant interaction between circadian period and pre- and post-sleep $F(1,12)=10.43$, $p < 0.007$. These results indicate that SRT performance immediately on awakening is worse than pre-sleep performance for both the normal circadian control night and the early circadian drug night, but that this "sleep inertia" (30) is worse for the early circadian sleep than for the normal circadian sleep.

The SRT trials from 15:00 h, 24:00 h, and 01:00 h of the early circadian drug night were submitted to the 2-way analysis of variance (comparison b) which revealed a significant main effect of trials ($p < .0001$). Post hoc analysis reveals that SRT performance at 15.00 h is better than at 24:00 h ($p < .0001$), SRT performance at 01:00 h is better than at 24:00 h ($p < .0001$), and there is no difference in performance between the SRT trials at 15:00 h and 01:00 h. This indicates that for the early circadian drug sleep, the impact of sleep inertia has totally dissipated by 01:00 h at which time performance returned to pre-sleep levels.

The SRT trials from 01:00 h to 07:00 h were submitted to final 2-way analysis of variance (comparison c). The results indicated no significant main effects or interactions. Essentially, SRT performance between 01:00 h and 07:00 h is sustained at pre-sleep performance levels, again with no drug effect.

Logical Reasoning Task (LRT): The LRT results are illustrated in **Fig. 5.** The pre-and post-sleep differences in logical reasoning were submitted to a 3-way repeated measures analysis of variance. There was no drug effect on LRT performance. There was however, a significant effect of circadian period $F(1,12)=10.64$, $p < 0.007$, and significant difference in pre- and post-sleep performance $F(1,12)=28.73$, $p < .0002$. These results (Fig. 5) demonstrate a sleep-inertia effect on LRT performance on awakening relative to pre-sleep performance for both the normal circadian control night and the early circadian drug night.

The LRT trials from 15:00 h, 24:00 h and 01:00 h of the early circadian drug night were submitted to the 2-way 'comparison b' analysis of variance which revealed a significant main effect of trials $F(2,24)=5.55$, $p < 0.004$. Post hoc analysis reveals that LRT performance at 15.00 h is better than at 24:00 h ($p < 0.004$), LRT performance at 01:00 h is better than at 24:00 h ($p < 0.02$), and there is no difference in performance between the LRT trials at 15:00 h and 01:00 h. These results indicate that for the early circadian drug sleep, the impact of sleep inertia on logical reasoning has totally dissipated by the 01:00 h.

The LRT trials from 01:00 h to 07:00 h were submitted to the 'comparison c' 2-way analysis of variance. The main effect of trials was significant $F(6,72)=2.49$, $p < 0.03$. The main effect of drugs was not significant, nor was the drug × trials interaction. This indicates that LRT performance changed over time between 01:00 h and 07:00 h but there were no differential effects on performance due to drugs. Polynomial analysis reveals that this trials curve was a significant quadratic function $F(1,38)=16.29$, $p < 0.0003$ with the point of inflection at 04:00 h. This indicates that LRT performance began to fall after 04:00 h, arguably due to fatigue but there was no differential fatigue effect across drugs. In order to illustrate this impact of fatigue, the logical reasoning performance between 01:00 h and 07:00 h is collapsed over drugs (because there were no drug effects) and plotted in **Fig. 6,** and a combined subjective fatigue index is super-imposed on these data. This combined subjective fatigue index was generated by averaging subjective fatigue data (from the Stanford Sleepiness Scale, as well as the mental and physical fatigue scales) shown in Fig. 3. By super-imposing this estimate of subjective fatigue onto the LRT performance it is possible to judge the relative effect of fatigue on performance. Like the three separate indices of subjective fatigue (Stanford Sleepiness Scale, mental and physical fatigue as illustrated in Fig. 3), the combined fatigue index for the trials between 01:00 h and 07:00 h also produces a significant cubic function $F(1,116)=22.77$, $p < .0001$. This cubic function reflects that the fatigue

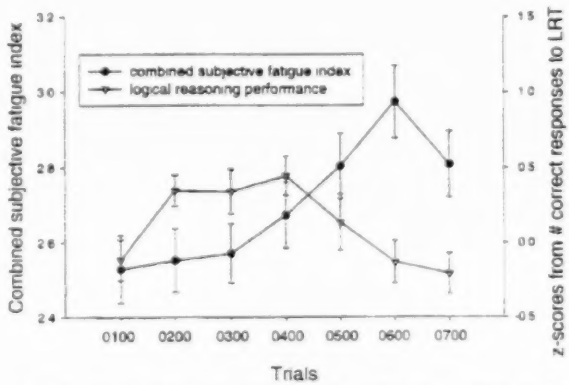

Fig. 6. Combined Subjective Fatigue Index super-imposed onto LRT performance during overnight psychomotor testing. All values are mean ± SEM.

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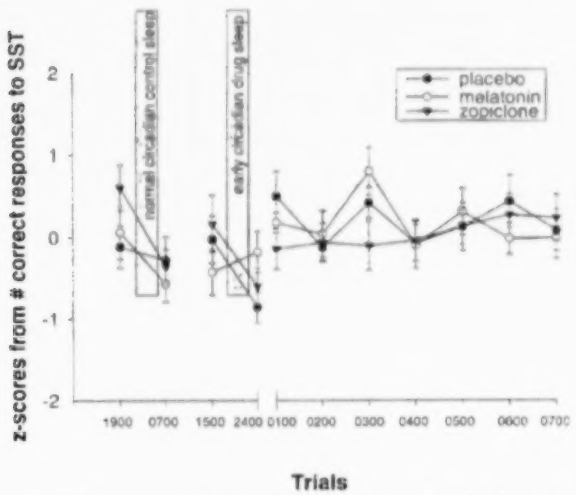

Fig. 7. *z*-scores for number of correct responses to Serial Subtraction task (SST) (mean ± SEM) plotted over drugs and trials for normal circadian control night and early circadian drug night

level is stable between 01:00 h and 03:00 h, after which it increases until 06:00 h, and then improves somewhat by the last trial at 07:00 h. In response to increasing fatigue levels, logical reasoning performance falls off after 04:00 h.

Serial Subtraction Task (SST): The SST results are illustrated in **Fig. 7.** The pre- and post-sleep differences in serial subtraction were submitted to the 'comparison a' 3-way repeated measures analysis of variance. There was no drug effect on SST performance for either medication. There was a significant effect in pre- and post-sleep performance $F(1,12)=7.73$, $p < 0.017$. These results demonstrate a sleep inertia effect on serial subtraction performance on awakening relative to pre-sleep performance.

The SST trials from 15:00 h, 24:00 h and 01:00 h of the early circadian drug night were submitted to the 2-way 'comparison b' analysis of variance which revealed a significant main effect of trials $F(2,24)=4.30$, $p < 0.025$. Post hoc analysis reveals that SST performance at 15.00 h is better than at 24:00 h ($p < 0.05$), SST performance at 01:00 h is better than at 24:00 h ($p < 0.009$), and there is no difference in performance between the SST trials at 15:00 h and 01:00 h. These results indicate that for the early circadian drug sleep, the impact of sleep inertia on serial subtraction performance has totally dissipated by the 01:00 h.

The SST trials from 01:00 h to 07:00 h were submitted to the 'comparison c' 2-way analysis of variance. There were no significant main effects or interactions. Performance on the SST between 01:00 h and 07:00 h remained unchanged throughout the period.

Multitask (MT): The MT results are illustrated in **Fig. 8.** The pre- and post-sleep differences in MT score were submitted to the 'comparison a' 3-way repeated measures analysis of variance. There was no drug effect on MT performance for either medication. There was a significant drugs × circadian period × pre- and post-sleep interaction $F(2,24)=4.95$, $p < 0.016$. This interaction indicates that on awakening from the normal circadian control night, MT performance was not impacted by sleep inertia for the subjects who were going to receive melatonin and zopiclone the following night. However, during the first psychomotor trial after awakening from the early circadian medicated sleep, there was a mild sleep inertia effect.

The MT scores from the 15:00 h, 24:00 h and 01:00 h trials were submitted to the 'comparison b' 2-way analysis of variance which revealed a significant main effect of trials $F(2,24)=3.46$, $p < 0.048$). Post hoc analysis indicates that the multitask performance at 24:00 h is worse than at 15:00 h ($p < 0.02$), and by 01:00 h MT performance is still worse than at 15:00 h ($p < 0.05$). Therefore the comparison b anova was repeated using the three original trials plus (15:00 h, 24:00 h, and 01:00 h) plus the 02:00 h trial. This iteration of the comparison b anova also indicated a significant main effect of trials $F(3,36)=3.38$, $p < 0.029$. In this instance, post hoc analysis indicates no difference in MT performance between the 15:00 h and the 02:00 h trials. This result indicates that while the sleep inertia during the MT was less than during the previous tasks (SRT, LRT, and SST) it did persist longer (until the 02:00 h trial).

The MT trials from 01:00 h to 07:00 h were submitted to 'comparison c' 2-way analysis of variance. There were no significant main effects or interactions. Performance on the MT between 01:00 h and 07:00 h remained unchanged throughout that period.

DISCUSSION

Sleep-induced decrements in performance immediately on awakening have been termed 'sleep-inertia' by Lubin et al. (27) who described sleep-inertia as 'reduced vigilance and impaired performance during the period that follows awakening. Sleep- inertia has been referred to as a phenomenon of impaired task performance and/or disorientation occurring immediately after awakening (29). Sleep-inertia effects have been ob-

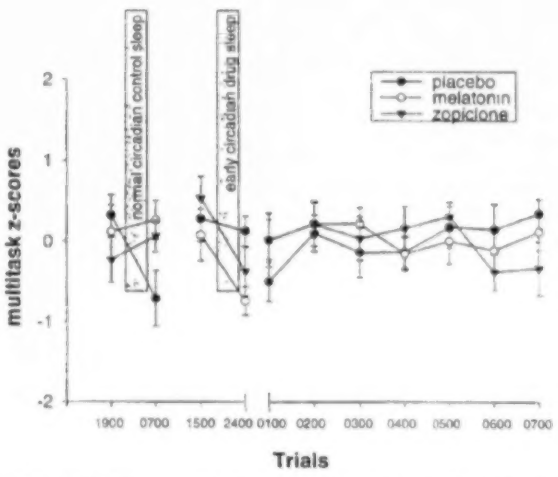

Fig. 8. Multitask *z*-scores (mean ± SEM) plotted over drugs and trials for normal circadian control night and early circadian drug night

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served on a range of psychomotor tasks (15): simple reaction time, complex reaction time, steadiness and coordination, visual perception tasks, memory tasks, time estimates, mental arithmetic, cancellation and clock reversal. The severity of sleep-inertia can vary as a function of sleep stage on awakening (15) and the amount of prior sleep deprivation (5). Estimates on the duration of sleep-inertia vary from 1 min (45) to more than 3 h (15). With no prior sleep deprivation, Wilkinson showed that sleep-inertia lasted a few minutes (48). However, Dinges et al. (16) showed that even after 56 h of sleep deprivation, sleep-inertia never exceeded 30 min.

In our study, the subjective manifestations of sleep-inertia are evident for all three parameters (Stanford Sleepiness Scale, as well as mental and physical fatigue ratings) (Fig. 3). The psychomotor manifestation of sleep-inertia was evident in all four tasks, but was most pronounced during the SRT task, perhaps because this was the first task performed by the subjects during each psychomotor test session. After the normal circadian sleep the subjects were awakened at 06:45 h and began the post-sleep psychomotor test session 15 min later at 07:00 h. After the early medicated sleep, the subjects were awakened at 23:45 h and began the post-sleep psychomotor test session 15 min later at 24:00 h. Subjective assessments of sleepiness and fatigue occupied the first minute of each psychomotor test session, after which the serial reaction task was presented to the subjects. The subjects, therefore, started the SRT task 16 min after awakening and finished it 19 min after awakening. Sleep-inertia effects on the LRT (which was presented to the subjects over the subsequent 3 min, that is, between 20 and 22 min after awakening) were not as strong as the effects on the SRT. The sleep- inertia effects on the SST (which occurred between 23 and 25 min after awakening) were even milder. Overall, the sleep-inertia effects on the three SUSOPS tasks were dissipated by the second test session after awakening (01:00 h). Sleep-inertia effects on the MT (a higher order cognitive task) appear to be equivocal on awakening from the normal circadian sleep, quite possibly because it was performed last in the test-battery sequence. After awakening from the early circadian medicated sleep, sleep inertia was evident during the MT, however it was milder than that seen during the preceding SUSOPS tasks. This lower level of sleep inertia during the MT persisted an extra hour relative to the duration of the sleep inertia during the SUSOPS tasks. We did not measure sleep stages, however it is possible that the subjects were waking from a deeper sleep stage at the end of the early circadian sleep period. Such a shift in sleep architecture could explain the potentiation of the sleep-inertia effect during the first post-sleep trial of SRT task after the early circadian sleep period. The duration of the sleep inertia effects in this study, appears to be consistent with the findings of other sleep-inertia researchers.

Comperatore et al. performed an influential study (11) on the effects of melatonin on aircrew. They demonstrated that 10 mg of melatonin improved sleep patterns and resulted in fewer errors on a choice reaction time task immediately after long range transmeridian flight. In subsequent work Comperatore and Kirby (12) performed 2 between group studies in an effort to determine aviator's grounding time after melatonin administration. In their second study, the subjects were given a 10 mg dose of melatonin or placebo for 5 d, awakened daily at 00:30 h after 8 h of sleep and were tested at 01:30 h, 03:30 h, and 06:10 h. The melatonin subjects made significantly more errors than the placebo subjects when tested at 01:30 h (1 h after awakening), but not in the 2 subsequent test sessions. In view of our own results, it is possible that the Comperatore and Kirby subjects were suffering from sleep inertia during the first post-sleep test session at 01:30 h.

With respect to the effects of zopiclone on performance, after a sleep period of 6 h and 45 min (7 h and 15 min after ingestion) we found the normal sleep-inertia effects but no differential effects across drugs. Our work thus supports the Griffiths et al. (19) work and various other studies (6,7,21,25,39,41,43) which were unable to demonstrate residual effects of zopiclone on various aspects of psychomotor performance.

Other than sleep-inertia, the only other impact on psychomotor performance in our study occurred during the logical reasoning task. While our protocol was not designed to cause significant fatigue, the increased levels of subjective fatigue (Fig. 6) reported by our subjects coincided with an attenuation of logical reasoning performance after 04:00 h. However there was no difference in performance across the drug treatments. In an earlier study (33), we found that the LRT was quite sensitive to fatigue.

Our work indicates that both melatonin and zopiclone were similarly effective facilitators of early circadian sleep. Also, neither of these medications altered the sleep inertia effects on psychomotor performance on awakening than placebo. Given that melatonin and Zopiclone provide more sleep than placebo during an early circadian sleep period, the expectation would be that psychomotor performance would be better after early circadian sleep on either melatonin or zopiclone than on placebo. In contrast with this expectation, we found performance after early circadian sleep on placebo was as good as that on either either melatonin or zopiclone. This would suggest that there is no performance benefit associated with getting more sleep by using melatonin or zopiclone. However, our protocol was designed to test for residual effects of either melatonin or zopiclone, but not to demonstrate an improved performance after sleep on either or these two medications. Certainly, if we had found residual performance effects associated with either melatonin or zopiclone, we would not be able to consider their operational use for aircrew. If our goal had been to show a psychomotor performance advantage with either melatonin or zopiclone, we would have stressed the subjects more by either running a longer post-sleep experimental period or by running multiple nights of early circadian sleep in order to develop a chronic fatigue state.

The melatonin dose we used (10 mg in a single capsule containing 5 mg of regular-release melatonin and 5 mg of sustained availability or time-released melatonin)

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is probably much higher than necessary to facilitate early circadian sleep. However, given that we have demonstrated no impact on psychomotor performance with this relatively high dose of melatonin, a lower dose should provide an extra margin of safety when used to facilitate aircrew sleep.

Based on their dose-response study Nicholson and Stone stated that the optimal clinical dose range of zopiclone is likely up to 7.5 mg. The 7.5-mg dose of zopiclone provides a useful hypnotic effect with minimal residual effects the next day, while "5.0 mg is the appropriate dose for those involved in skilled tasks where even the most minor changes in performance during the early part of the day must be avoided" (30,31). While the 7.5-mg zopiclone dose we used in this study indicates no residual effects on performance, in the interests of flight safety, we will heed the advice of Nicholson and Stone by using a smaller dose in a follow-on operational evaluation. In such an operational evaluation we will use 5.0 mg of zopiclone and 2 mg of time-released melatonin in order to determine their relative efficiency at facilitation of early circadian sleep during long-range transmeridian air transport operations.

CONCLUSIONS

The melatonin and zopiclone doses used in this study have been shown to facilitate early circadian sleep relative to placebo. While we have documented normal, transient, sleep-inertia effects on arising from sleep, there is no indication of any impact of either melatonin or zopiclone on psychomotor performance after sleep in the dosages we used.

ACKNOWLEDGMENTS

The efforts of Gordon Kenny are most gratefully acknowledged. His relentless efforts to ensure quality data collection during a very long and very tiring protocol were most inspiring. Further, his data reduction expertise saved many days of toil. The conscientious data reduction efforts of Tim Mandzak and Victor Mota are also gratefully acknowledged. Ms Nadine Fidler provided us extensive technical assistance during the busy period leading up to the commencement of our study. Her expertise and commitment are gratefully acknowledged.

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